Review

Randomized Controlled Trials in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis

Rachel L. Police,[1] Peter C. Trask,[2] Jianmin Wang,[3] Robert Olivares,[4] Shahnaz Khan,[3] Adeline Abbe,[4] Ann Colosia,[3] Annete Njue,[5] Beth Sherrill,[3] Rodrigo Ruiz-Soto,[6] James A. Kaye,[1] Mehdi Hamadani[7]

Abstract

This systematic literature review with meta-analysis was conducted on the clinical efficacy and safety of interventions used in the treatment of chronic lymphocytic leukemia (CLL). We systematically searched databases (PubMed, Cochrane Library, and Embase; 1997 to August 2, 2012), conference abstracts, bibliographic reference lists, recent reviews, and Clinicaltrials.gov. Primary efficacy outcomes were objective response rate, progression-free survival, and overall survival. Safety end points were Grade 3/4 toxicities, serious adverse events, withdrawals because of toxicity, and deaths due to toxicity. Studies were selected if they were randomized controlled trials (RCTs) reporting on the efficacy or safety of relapsed or refractory CLL and if outcomes for CLL were reported separately from trials that included other lymphoid neoplasms. We used the Bucher method for conducting adjusted indirect comparisons within a meta-analysis. We identified 6 RCTs of pharmacologic treatment for relapsed/refractory CLL. The most common drugs investigated (alone or in combination) were fludarabine and cyclophosphamide. When reported, median overall survival ranged from 27.3 to 52.9 months, and overall response rate from 58% to 82%. Although meta-analysis of efficacy results was considered, details are not presented because only 3 studies qualified and the common comparator treatment was not clinically relevant. The relatively small number of RCTs, few overlapping treatment arms, and variability in end points studied make it difficult to formally compare therapies for relapsed/refractory CLL. Significant variability in RCT features presents a further challenge to meaningful comparisons. Additional well-designed RCTs are needed to fully understand the relative efficacy and safety of older and more recently developed therapies.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most frequently occurring subtype of leukemia, with an age-adjusted annual incidence of 4.65 per 100,000 persons in the United States.[1] The incidence of CLL is greatest in older individuals (average age, 72 years), and it occurs nearly twice as frequently in men than in women.[1,2] CLL is now combined with small lymphocytic lymphoma as a mature lymphocytic neoplasm subcategory in the World Health Organization classification because the 2 entities are considered biologically to be the same disease with different clinical presentations.[3]

Since the 1990s, advances in immunochemotherapy have led to substantial improvement in the prognosis of patients diagnosed with CLL. In particular, the development and use of the monoclonal antibody rituximab as monotherapy in initial treatment, and in combination with bendamustine and other chemotherapies (eg, cyclophosphamide, vincristine, doxorubicin, prednisone) in relapsed or refractory (R/R) patients, has led to longer survival times. Despite these advances, most CLL patients relapse after

[1]RTI Health Solutions, Boston, MA
[2]Global Evidence and Value Development, Sanofi, Cambridge, MA
[3]RTI Health Solutions, Research Triangle Park, NC
[4]Global Evidence and Value Development, Sanofi, Chilly-Mazarin, France
[5]RTI Health Solutions, Manchester, United Kingdom
[6]Oncology Research and Development, Sanofi, Cambridge, MA
[7]Medical College of Wisconsin, Milwaukee, WI

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Address for correspondence: Peter C. Trask, PhD, MPH, Global Evidence and Value Development, Sanofi, Cambridge, MA 02142
E-mail contact: Peter.Trask@sanofi.com

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first-line chemotherapy.[4] Treating R/R disease represents a major treatment challenge. Diminished response rates to rituximab in patients with previous rituximab treatments have been observed in multiple lymphoid neoplasms.[4] Although fludarabine is a cornerstone of first-line therapy for CLL, up to 37% of patients with fludarabine-refractory disease will not respond to single-agent fludarabine as a salvage therapy, although that proportion decreases to 10% if fludarabine is combined with rituximab.[5,6]

Several published randomized controlled trials (RCTs) have assessed various therapeutic regimens in patients with R/R CLL; however, we are not aware of any published systematic review or meta-analyses of the evidence that is currently available. Thus, this study assembled available information on the clinical efficacy and safety of treatments used in patients with R/R CLL and attempted a meta-analysis of key efficacy outcomes. We were particularly interested in whether there were treatments (chemotherapy or chemoimmunotherapy) that had better efficacy and safety than others and should be recommended as a standard against which to test drugs in development.

Methods

Literature Search and Data Extraction

The work reported here was part of a larger effort to review current treatments for several forms of indolent non-Hodgkin lymphomas (NHLs), including CLL. Three electronic databases (PubMed, Embase, and the Cochrane Library) were systematically searched for studies on the efficacy and safety of treatments for R/R indolent NHL published in English from January 1, 1997, to August 2, 2012. Additional sources were identified through searches of conference proceedings from the 2011 and 2012 meetings of the American Society of Clinical Oncology (ASCO), the European Hematology Association, and the 2010 and 2011 meetings of the American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO), the Clinicaltrials.gov database, and the bibliographies of included trials and recent reviews.

To identify studies on the broad array of disease states of interest for the larger NHL project, synonyms for indolent B-cell NHL were used. Because this study was also conducted alongside 2 reviews on diffuse large B-cell lymphoma and mantle cell lymphoma, synonyms for those disease states were included in the initial search strategy. Search terms included combinations of medical subject heading (MeSH) and disease terms limited to the title and abstract. The search was restricted using MeSH and title and abstract terms for interventions, particularly pharmacotherapy. The search was also restricted to clinical studies. Supplemental Table 1 (in the online version) presents the specific search strategy for PubMed.

Inclusion or exclusion of studies was assessed independently in 2 steps by 2 researchers. At level 1, titles and abstracts of all identified articles were screened. The full texts of all records determined to be eligible at level 1 were reviewed at level 2 to ensure that they met the inclusion criteria. All disagreements were resolved by consensus, with input from an experienced senior researcher if necessary. Articles were included at level 1 if they described randomized or nonrandomized clinical studies evaluating chemotherapy in patients aged 18 years or older with R/R NHL.

Because a meta-analysis was initially planned, and because RCTs generally provide the strongest evidence of comparative efficacy (and safety), a decision was made to focus only on RCTs. At level 2, only RCTs evaluating the efficacy or safety of pharmacologic therapy in patients with R/R CLL were included. A final review excluded all RCTs that were not conducted in patients with CLL. Because autologous stem cell transplant was not a treatment of interest at level 2, RCTs that presented outcomes of transplant programs that did not separately present the short-term outcomes related to conventional-dose chemotherapy preceding high-dose transplant-preparative chemotherapy were excluded.

Full data extraction was performed on all RCTs that passed the 2 levels of screening. Extracted outcomes included trial and demographic characteristics, overall response rate (ORR), complete response, partial response, duration of response, median progression-free survival (PFS), median overall survival (OS), withdrawals because of adverse events (AEs), deaths due to toxicity, serious AEs (SAEs), and Grade 3 or 4 AEs.

Because the specific objective for the review presented here was to evaluate the efficacy and safety of treatments in patients with R/R CLL, study outcomes were not reported if those outcomes were not presented separately for the naive and R/R populations in the source publications. Likewise, if a trial included patients with other lymphoid neoplasms and CLL but did not present results stratified according to disease category, results for patients with CLL could not be included in our analysis.

Assessment of the methodological quality of the included RCTs was based on guidance in the National Institute for Health and Care Excellence Single Technology Appraisal specification for manufacturer/sponsor submission of evidence 2009[7] and adapted from the Centre for Reviews and Dissemination guidance for undertaking reviews in health care.[8] Parameters assessed included randomization, masking of patients and clinicians, concealment of treatment allocation, similarities between treatment groups at baseline, documentation of dropouts, and intent-to-treat analysis.

Meta-Analysis

Unique trials were identified from the complete list of identified articles. RCTs that included at least 30 patients were considered for inclusion in the meta-analysis, providing that they had at least 1 treatment arm in common with at least 1 other trial. Where data were available, end points that were analyzed for patients with CLL included complete or partial ORR, PFS, OS, and AE rates. Because hazard ratios (HRs) were not consistently reported, the difference of median PFS between 2 treatments and its variance was estimated for use in the meta-analysis. Because of the scarcity of comparative data available, comparisons were planned to be made using the simple adjusted indirect comparison method,[9] the Bucher method, which is a fixed-effect approach. It might have been technically possible to fit a mixed-treatment comparison model to objective response rate and AEs and to evaluate random study effects; however, this approach was not used because no studies involving direct comparisons were available to contribute to the models.

Results

Systematic Literature Review

A total of 3216 unique records were obtained through the electronic database searches for the broader indolent NHL review